associated pathologies associated with T cell mediated autoimmune diseases. Rather, the prior art that relates to gp39 antagonists for therapy is limited in its teachings to the use of a gp39 antagonist to inhibit T cell induced B cell activation, and thereby inhibit humoral immunity. Also, the prior art does not "inherently" suggest that a gp39 antagonist could be used to effectively treat a T cell mediated autoimmune disease by suppressing mediated cellular immune response.

In any event, this rejection should be moot in view of the cancellation of claims 13-17, in view of the fact that the "inherency" based on §103 rejection now is clearly unsustainable and therefore must be withdrawn.

Turning now to the Office Action, the informality with respect to claim 22 is corrected herein.

The prior art rejection of claims 13-16 under §103 is moot in view of the cancellation of these claims. Likewise, the prior art rejection of claims 13 and 17 based on §103 is moot in view of the cancellation of these claims herein. The only outstanding rejection is that of claims 13-26 (now claims 18-26 in view of claims 13-17 being cancelled).

Specifically, claims 18-26 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Lederman et al. (U.S. Patent No. 5,993,816) and/or Armitage et al. (U.S. Patent No. 6,264,951), in view of Schieven (U.S. Patent No. 5,565,491), Stull et al. (Cell. Immunol. 117:188-198, (1998)) and Flynn et al. (Cell. Immunol. 122:377-390 (1989)) (with respect to thyroiditis) and/or Tung et al. (Clin. Immunol. Immunopathol. 73:275-282, 1994)) and Rabinowe et al. (Am J. Med. 81: 347-350 1986)) with respect to oophoritis. This rejection is respectfully traversed.

Essentially the basis of the rejection is that Lederman et al. and Armitage et al. teach the use of gp39 antagonist including anti-gp39 antibodies for treating autoimmune diseases but do not explicitly mention either oophoritis or thyroiditis. However, the Office Action suggests that this deficiency is overcome by the secondary references. This rejection is respectfully traversed.

The primary references Lederman et al. and Armitage et al. do not expressly or inherently teach or suggest the invention. As argued previously, these patents only suggest the use of a gp39 antagonist to suppress humoral immunity. Moreover, while in their list of autoimmune diseases there is incidental mention of some T cell mediated autoimmune

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diseases (e.g. diabetes) there is absolutely no suggestion that a gp39 antagonist could be used to inhibit cellular immune responses (non-humoral) elicited by T cells which are responsible for the tissue destruction, inflammation and other pathological responses that occur during T cell mediated autoimmune diseases. Rather, the only conclusion that reasonably can be drawn from the Lederman and Armitage patents is that gp39 antagonists can be used to suppress humoral immunity and treat diseases wherein B cells and specifically antibodies are significant in the disease pathology.

By contrast, both thyroiditis and oophoritis are classic examples of T cell mediated autoimmune diseases. Therefore, neither Lederman nor Armitage would expressly or inherently suggest that either of these autoimmune disease could be effectively treated by use of a gp39 antagonist. Moreover, the secondary references likewise do not suggest the claimed methods of treating thyroiditis or oophoritis.

Schieven is cited based on its disclosure that phosphotyrosine inhibitors can be used to control the proliferation of B cells wherein the downregulation of the immune response is desirable, and for its disclosure that such inhibitors can inhibit antibody responses mediated by CD40/gp39. Based thereon, the Examiner suggests the use of a gp39 antagonist would be obvious. However, this rejection is respectfully traversed on the basis that it ignores the fact that thyroiditis is widely regarded to be a classic example of a T cell mediated autoimmune disease. Therefore, while this reference suggests that suppression of B cell proliferation possibly may be used to intervene in autoimmune diseases including a type of thyroiditis (Hashimoto's), it does not fairly suggest that a gp39 antagonist would be suitable for treating thyroiditis. Essentially, the reference does not provide any reason to believe that tissued destruction attributable to cellular mediated immune responses which are elicited by T rather than B cells would be inhibited. Absent a reason to believe that this would occur, Schieven does not teach or suggest the claimed therapeutic methods alone or in combination with Lederman or Armitage which also do not suggest the use of a gp39 antagonist to suppress T cell mediated cellular immune responses.

Likewise Stull et al. does not teach or suggest the claimed methods alone or in combination with the already-discussed references. Stull is cited based on its disclosure that an anti-L3T4 antibody blocked the activation of T helper cells and "might be effective in therapy of autoimmune diseases in humans". This basis of the rejection is respectfully

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traversed on the basis that it deals with an antibody to a different antigen (L3T4) and is speculative. Essentially, whether an anti-L3T4 antibody reversed experimental thyroiditis in an animal model does not fairly suggest that an anti-gp39 antibody would behave similarly. This is notwithstanding the fact that this antibody targeted similar cells. To the contrary, the possible effect of an antibody that targets a different antigen is not probative of the therapeutic effects of an antibody that targets a completely different antigen. This rejection is clearly predicted on the improper "obvious-to-try" standard as the possible therapeutic effect of an anti-L3T4 antibody does not suggest that an anti-gp39 antibody would behave similarly, irrespective of the fact that it binds an antigen on activated T cells.

The same arguments apply for the Flynn et al. reference. Again, this reference suggests the effects of an anti-L3T4 antibody on helper T cells. Specifically, the reference suggests that this antibody depleted helper T cells and may inhibit the development of thyroiditis. However, this does not fairly suggest that an anti-gp39 antibody would have a similar effect, namely T cell depletion, or that this would correlate to an effective treatment for thyroiditis. Essentially, Applicants maintain that the effect of an antibody that binds a completely distinct antigen (L3T4) from gp39 cannot be used to predict the therapeutic efficacy of an anti-gp39 antibody, much less that it would elicit a similar T cell depleting effect. In fact, the mechanism by which anti-gp39 is effective is by suppressing T cell immune responses by the induction of T cell tolerance. This is not fairly suggested by any of the cited references in the content of treating thyroiditis with an anti-gp39 antibody.

Tung et al. is cited based on its disclosure that the transfer of $CD4^+$ T cells can transfer autoimmune oophoritis in animal models and that these cells may contribute to the formation of auto-antibodies.

Rabinowe et al. further teaches that T cells contribute to immune dysfunction in oophoritis and that this may explain why immunosuppressive corticosteroid therapy has some efficacy in treating this disease.

Based on Rabinowe et al. and Tung et al., the Office Action suggests that treating oophoritis using a gp39 antagonist would have been obvious. This rejection is respectfully traversed.

Again the rejection is based on the improper "obvious-to-try" standard and further is improper as it attempts to read information into the primary references which simply is not

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there. Essentially, whether Tung et al. or Rabinowe et al. teach that T cells are involved in oophoritis and that blocking T cell responses may provide a mechanism for treating the disease does not suggest that a gp39 antagonist would suppress T cell associated pathological responses in oophoritis. It is a huge and unrealistic leap from the prior art suggestion that corticosteroid may be effective in oophoritis (based on their beneficial effective in oophoritis therapy) and that T cells transfer the disease in experimental animal models of oophoritis to extrapolate that a gp39 antagonist could be used to effectively intervene in the treatment of oophoritis.

Contrary to the rejection, the references singularly or in combination do not provide a reasonable expectation of success. In fact, had the role of gp39 antagonists in suppressing T cell function been "reasonably expected" it certainly would have been mentioned in the primary references, Lederman et al. and Armitage et al. However, it is not.

Thus, based on the foregoing, Applicants respectfully maintain that the §103 rejection should be withdrawn because (i) the inherency-based rejection is not applicable as the prior art does not inherently teach the use of a gp39 antagonist for the claimed therapies and (ii) the prior art does not provide a reasonable expectation of success and in fact is predicated as the improper "obvious-to-try" standard.

Accordingly, based on the foregoing, withdrawal of the §103 rejection of claims 18-26 based on Lederman et al. and/or Armitage et al. in view of Schieven, Stull et al., Flynn et al., and/or Tung et al. and Rabinowe et al. is respectfully requested.

It is anticipated that this response should place this case in condition for allowance. A Notice to that effect is respectfully solicited.

Respectfully submitted,

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Appendix

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APPENDIX

22. (Amended) A method for treating ~~thyroluitis~~ thyroiditis comprising administering a therapeutically effective amount of a gp39 antagonist selected from the group consisting of an anti-gp39 antibody or fragment thereof that binds gp39, soluble CD40 and a CD40 fusion protein.